Chapter 1
Introduction and scope of the thesis

In this thesis the relation between central serotonergic neurotransmission and behavioral correlates are investigated. The serotonergic system has been subject of psychiatric research and speculation for over 5 decades. Traditionally deficient serotonergic function is associated with depression but currently the role of serotonin in virtually any psychiatric disorder is recognized. Serotonergic neurons project extensively onto many brain regions and the anatomy of these projections show remarkable similarity across species. So, the serotonergic system is a phylogenetically old system. Although the system is involved in many physiological processes it is the sole mediator of none of them. These properties indicate that the system plays a modulative role in brain function.
Initially, the involvement of the serotonergic system in psychiatric disorders has shifted attention from its role in human non-pathological states. However, since modulation of the system is widely used to alleviate psychiatric symptoms, gaining insight into the physiology of the system may contribute to rationalisation of psychiatric treatment.
Release of serotonin in the brain is highly dependent on plasma levels of its precursor tryptophan. After acute dietary depletion of tryptophan divergent behavioural effects have been observed in psychiatric patients and healthy volunteers. Longer lasting depletion of plasma tryptophan levels in non-psychiatric populations might result in more pronounced symptoms unbiassed by psychiatric diagnosis. We studied patients suffering from somatic diseases leading to modulation of plasma tryptophan levels and thus brain serotonin levels. In this way, chronic disturbances of the serotonergic system could be studied. Furthermore, these patients made it possible to study the circumstances in which the serotonergic system is compromised providing insight in the (patho)physiological role of the system. We focused on the possible role of serotonin as a link between somatic disease and associated psychological states. This subject has been further investigated through literature research.

In chapter 2 an overview is given of existing literature on the modulation of plasma tryptophan levels in somatic states. Several pathophysiological mechanisms of tryptophan depletion and the possible consequences for behaviour and emotional wellbeing are described. In chapters 3 and 4 the psychiatric and cognitive profiles of carcinoid patients have been investigated. Carcinoid tumours are marked by intermittent peripheral production of large amounts of 5-HT. In this way, the chronic consequences of plasma tryptophan fluctuations could be studied. In chapter 5 tryptophan catabolism under the influence of induced inflammation and the behavioural consequences of this is described. In chapter 6 the treatment we performed in 3 patients is described. In chapters 7 and 8 the consequences of administration of endotoxin on tryptophan catabolism in animals and healthy volunteers are illustrated. A model of tryptophan depletion in infectious circumstances are thus provided. Finally, in chapter 9, an overview is given of the cicumstances and consequences of modulation of plasma tryptophan levels across species. This gives some insight in the physiological meaning of plasma tryptophan fluctuation. This is followed by a general discussion.